REMARKS

On November 9, 2004 Applicants' undersigned attorney conducted an interview with SPE Gary Kunz. During the interview, undersigned counsel detailed why the Depui reference does not contain disclosure so as to enable one of ordinary skill to provide a formulation wherein the dosage form is stabilized in the absence of a separating layer. Attention was invited to the comparative data set forth in Example 1, Tables 1 to 3 of the Lovgren '505 patent. This data shows that prior art formulations not containing a separating layer, but containing an active ingredient within the scope of that recited in the now pending claims, experienced rapid degradation of the active ingredient. Example 1 of Lovgren '505 contains no disclosure as to whether the active ingredient was in the form of an active layer, as recited in the now pending claims, or was in a core formed by an extrusion process wherein the active ingredient and all the core excipients were intermixed. Since Example 1 of the '505 patent refers to tablets, one may well conclude that the active ingredient is within the core rather than in a drug containing layer.

Applicants also expressed concern as to the manner in which the previously submitted Molina Declaration was addressed. Because of the lack of detail or exemplification of any embodiment of a dosage form without a separating layer in the Depui reference, Applicants had provided a form of comparison to other prior art (Takeda) which contained more detail and which dealt with these types of compounds. The Examiner was again referred to the differences in stability. Even though the Molina Declaration was submitted more than 2 years ago, the Examiner has yet to substantively address that declaration. Rather, the Examiner in the March 2005 Office Action now states that the demonstration of the Molina Declaration is moot. It is respectfully submitted that the Examiner is in error. Perhaps the Examiner does not fully appreciate Applicants' prior submitted explanation of the significance of EP 0642797 to the anticipation rejections based on the Depui references.

I. THE ANTICIPATION REJECTIONS

In the Office Action of March 4, 2005, claims 1 to 13, 26 to 29, 37 and 38 were rejected under 35 U.S.C. 102(e) as anticipated by U.S. Patent No. 6,132,771 to Depui et al. ("Depui '771"). It is submitted this rejection is in error as a matter of law and should be withdrawn.

It is a fundamental principle of the U.S. Patent Laws that for a reference to anticipate a claimed invention, that single reference must show each and every feature of the claimed invention arranged as in the claim. See *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193 (Fed. Cir. 1993). That reference must contain sufficient disclosure as to convince one of ordinary skill in the art that the inventor had possession of the invention at the time the reference was filed. When a composition is claimed, an anticipating reference must completely identify the claimed composition, as it is set forth in the claim, and must also provide an enabling disclosure so that one of ordinary skill in the art can, without undue experimentation, practice the invention. See *In re Sheppard* 144 U.S.P.Q. 42 (CCPA 1964). If a reference fails to properly identity the invention or to enable one to make the invention without undue experimentation, that reference does not describe the invention and cannot be an anticipatory reference.

It is submitted that the Depui '771 reference does not anticipate the now claimed invention as a matter of law. It neither identifies the claimed invention, nor does it enable one of ordinary skill in the art to make the invention without undue experimentation.

The Depui '771 patent, assigned to Astra-Zeneca, is directed to an oral pharmaceutical dosage form for a combined therapy against GORD (Gastro Oesophageal Reflux Disease). The dosage form is preferably a tablet containing an acid suppressing agent (proton pump inhibitors i.e. omeprazol, lansoprazol,...) and a prokinetic agent (i.e. cisapride, mosapride,...).

A. Depui '771 Fails to Identify the Claimed Invention

Depui never discloses or suggests that the active containing layer is substantially non-porous. See line 3 of pending claim 1. Importantly, the rejection of March 2005 does not state, or suggest, that Depui '771 shows or suggests this feature of the now claimed invention or point out where Depui shows or suggests this feature. The reference's examples merely refer to the active layer being applied to the seed. There is not a single example, suggestion, description or mention in Depui '771 of a stable and useful composition or composition with a substantially non-porous active layer as defined in the presently pending claims.

All 14 examples of Depui refer to a proton pump inhibitor dosage form having an alkaline substance and/or at least one separating layer between the active containing region and the surrounding enteric coating. The alkaline substance can be included as a basic salt of the corresponding proton pump inhibitor, i.e. omeprazole magnesium salt, as stated in the '505 (col. 4, lines 23 to 27) and '230 (col. 8, lines 55 to 61) patents.

Accordingly, Depui '771 fails to identify the invention as claimed and thus the anticipation rejection is in error as a matter of law.

B. Depui '771 Fails to Enable the Claimed Invention

In column 2, starting at line 47, Depui '771 describes as obvious that the proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer and specifically refers to U.S. Patent No. 4,786,505 ("the 505 patent") for omeprazole preparations (see col. 2, lines 50-57) with a description of enteric coating layered preparations of proton pump inhibitors.

The '505 patent discloses omeprazole pellets having a core containing omeprazole and an alkaline substance, one or more separating layers, and an outer enteric coating. The separating layer(s) are described as necessary because: *"The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discoloration*

of omeprazole during the coating process or during storage."(see '505 col. 3, lines 4-8). U.S. Patent No. 4,853,230 (the '230 patent), contains similar disclosure relating to other proton pump inhibitors (see col. 8, line 67 to col. 9, line 4).

Both the '505 (col. 3, lines 36 to 65) and the '230 (col. 8, lines 31 to 61) patents refer to the importance of the presence of an alkaline substance and both contain extensive disclosure as to the necessity of the separating layer because of the acid sensitivity of omeprazole and other so called acid labile compounds (benzimidazoles) and the negative experiences in bio-studies of benzimidazole compositions without the separating layer. The '505 patent refers to an article "Development of an Oral Formulation of Omeprazole", Scand. J. Gastroenterology, 1985, pgs. 113-120 describing conventional enteric coated dosage forms and their stabilization. The '505 patent also contains an example (Example 1) comparing the stability of tablets with and without separation layers. According to the '505 patent, those dosage forms without the separating layer showed poor and unacceptable stability.

Depui '771 fails to describe how a stable and useful oral dosage form of a proton pump inhibitor can be made without having at least one separating layer. That is to say, even if Depui contained sufficient disclosure to identify the now claimed composition, Depui fails to contain enabling disclosure as to how to make such a composition.

The Examiner has referred to text in the reference calling the separating layers(s) "optional". However, that "optional" feature is referred to only generally and it is not supported by the cited prior art or by the patent description. Since the main object of Depui '771 is a combined therapy for GORD, the patentee sought broad protection and attempted to foreclose others from patenting a composition with no separating layer by a non-informative characterization of such a feature as "optional". However, Depui fails to even hint at how a useful and stable enteric coated dosage form can be made without one or more separating layers.

It is submitted that referring to a possible embodiment as "optional" is not a disclosure or description of embodiments employing or failing to employ the "option". This is especially true where, as here, the

specification contains no written description of such an embodiment, no enabling disclosure of how to make or use the "optional" embodiments and, not only fails to provide a best mode, but fails to disclose any mode with respect to that embodiment.

A mere mention of a possible embodiment is not sufficiently definite or particular that, without undue experimentation, one of ordinary skill in the art can gain possession of the claimed subject matter based on the reference disclosure. See, *Sheppard*, supra. at page 45. Characterizing a feature as "optional" does not identify the invention or convey to one of ordinary skill in the art that the inventor had possession of that embodiment. Accordingly, the Depui disclosure is not enabling to prepare stable and useful proton pump inhibitor oral dosage forms without having at least one separating layer. Hence there can be no anticipation.

If the Examiner is of the view that one of ordinary skill could follow the Depui examples and just omit the steps leading to the inclusion of the separating layer[1], the record contains a sufficient showing of the fallacy of this position.

The prior submitted Molina Declaration and discussion of Example 1 of Lovgren '505 are relevant to this point. The Molina Declaration illustrates that a prior art reference (Takeda) which purports to produce a stable granule or pellet containing a benzimidazole without a separating layer does not in fact do so. The Molina Declaration also illustrates that based on that prior art reference (Takeda), it would require undue experimentation even though Takeda purports to disclose an enabling process. Here Depui does not purport to disclose an enabling process. Also see the discussion of the composition of certain of the Depui '771 Examples and the '505 Examples under the discussion of the obviousness rejection, *supra*.

Applicants submit that since Depui '771 never exemplifies an embodiment without a separating layer and the prior art (Lovgren '505) and the Molina Declaration show prior art failure, there is no reasonable basis in the record to believe such an unenabled embodiment would be successful. See, *In re Dow Chemical Co.*, 5

[1]Applicants believe that the Examiner has acknowledged the obvious, that Depui does not illustrate how one would prepare a stable dosage form without a separating layer.

U.S.P.Q. 2d 1529 (Fed. Cir. 1988). Accordingly, the Examiner is again called upon to comply with the provisions of 37 C.F.R. 1.104(d)(2). This request was repeated by Applicants in the Response of December 2004 but again not addressed in the Office Action of March 4, 2005 wherein the claims were finally rejected.

Submitted herewith is the Declaration of Mona Johansson Under Rule 132. In this Declaration, the declarant reports that she has reproduced the first step of Example 5 of the Depui '771 patent to obtain enteric coated pellets but has conducted that Example without the addition of a separating layer.

As pointed out in the Johansson Declaration, since Example 5 does not specifically include a procedure, declarant employed procedures set forth in Example 1 of Depui '771. Also, as observed by the declarant, both Examples 1 and 5 lack many technical details and the declarant has relied on her professional knowledge and skill in this field to supplement the missing details.

As pointed out at the top of page 3 of the Declaration, the enteric coated pellets without a separating layer quickly became discolored. As can be ascertained from U.S. Patent No. 4,786,505, the discoloration is an indication of degradation of the active ingredient. The remainder of the sample pellets referred to in the Johansson Declaration will be discussed with respect to the rejection for obviousness. However, it is clear that the Examiner's theory that one can just omit a separating layer in the procedures of Depui and yet obtain a stabilized pharmaceutical dosage form of the benzimidazole compounds is clearly wrong as shown in Example 1 of Lovgren '505, the Molina Declaration and now the Johansson Declaration.

Applicants' submit that the Johansson showing alone or in combination with either of, or both of, the Molina Declaration and Lovgren '505 patent establishes that the Depui references are not enabling with respect to an embodiment wherein there is no separating layer between the active containing layer and an enteric coating for the benzimidazole compounds. Accordingly, the rejections under 35 U.S.C. §102 are in error as a matter of law.

Claims 15 to 25, 30 to 34, 36, 39 and 40 were rejected under 35 U.S.C. 102(e) as anticipated by U.S. Patent No. 6, 365,184 to Depui et al. ("Depui '184"). It is submitted this rejection is also improper as a matter of law and should be withdrawn.

The Examiner's statement of rejection for these claims is essentially the same as that based on Depui '771 except the Examiner now refers to Example 4 stating that "the examples utilize Wurster-type fluidized apparatus to coat the active agent onto the sugar core, followed by enteric coating".

Applicants repeat the above stated comments with respect to this rejection also. Further, Example 4 of Depui refers to an embodiment wherein the layering with the active was performed in an apparatus other than the Wurster fluid bed. Subsequently, a subcoating layer was applied to the layered core before the enteric coating layer was applied. Depui '184 also refers to an embodiment where other active ingredients (such as naproxen) were included in the formulation. Once again, the process used is not fully disclosed and there is no mention of conditions of operation. Accordingly, this rejection is also in error as a matter of law.

Applicants above showings and comments regarding Depui '771 (lack of identity and enablement) are incorporated herein. Applicants submit that Depui '184 does not, as a matter of law, anticipate claims 15 to 25, 30, to 34, 39 and 40.

II. THE OBVIOUSNESS REJECTIONS

Claims 1 to 13 and 15 to 40 have been rejected under 35 U.S.C. 103(a) as patentable over Depui '771. See the Official Action at pages 6 to 7. It is submitted the rejection is improper and should be withdrawn. In the discussion of the Depui '771 disclosure as applied to the preceding claims, the Examiner never addresses the nature of the claimed active containing layer.

After discussing the disclosure of Depui '771, the Examiner concludes that one of ordinary skill in the art would have been motivated to make an oral composition comprising an inert core, an active coating, and an enteric coating without the presence of a separating layer based on the reference and the expected result would be a successful composition for the treatment of gastrointestinal disorders. However, the Examiner

never sets forth what criteria or what basis there is to believe that the resulting composition would be "successful".

Applicants have submitted extensive material showing that one would have expected to the contrary. That is to say that in the absence of the separating layer, the composition would not be expected to be "successful". To the contrary, based on the submissions, one would have expected a composition wherein a substantial portion of the benzimidazole was degraded, i.e. a failure. This is because as discussed above, Depui '771 does not contain a single example that prepares such a composition and contains no information as to how such a composition would actually perform and relevant art teaches that a supporting layer is necessary to avoid degradation of the active ingredient. Curiously, Depui does not even include stability information in the formulations of the 14 examples. Applicants again repeat their request that the Examiner comply with 37 C.F.R. 1.104(d)(2).

It appears that the Examiner's entire basis for asserting motivation is the word "optional" in the '771 specification. However, under the circumstances, such is not sufficient.

Applicants submit there is a proper side by side showing of record by the comparison of Depui's examples with the examples of the Lovgren '505 patent. Applicants have previously submitted a chart comparing example 9 of Depui '771 with Examples 7, 8 and Comparative Example V of the '505 patent. A comparison of the method to produce magnesium omeprazole pellets of Example 9 of Depui '771 and the method to produce the pellets of Examples 7 and 8 of the '505 show that the **processes are identical** in those references. See previously submitted ***Annex 2***. (Amendment of June 26, 2003). The core material of Depui's '771 Example 9 has the same ingredients as the core material of Example 7 ('505 patent), the only difference being the ratio of magnesium omeprazole versus diluents, which is higher in Example 9. In both cases the core material is covered with hydroxypropylmethylcellulose ("HPMC") and the percentage of the polymeric film forming material used in the separating layer is essentially the same (11 and 10% respectively). Finally, pellets having a separating layer are further coated with an enteric polymer and the ratios of that polymer used in the

enteric layers in both examples are essentially the same (11 and 10%, respectively). In order to calculate the % of methacrylic acid copolymer, one can assume that the material used is 100g of a 30% aqueous suspension of the polymer. The formulation of Example 8 of the '505 patent is the same formulation of Example 7, wherein part of the mannitol diluent has been substituted by magnesium hydroxide.

As stated in column 13, lines 40 to 65 of the '505 patent, the formulation of the Comparative Example V is the same as in Example 8 but no subcoating layer is used and the pellets are prepared as described in Example 2 of the '505 patent.

Annex 3 of the June 2003 Amendment is a chart comparing Example 14 of the Depui '771 with Examples 2, 3, 4 and Comparative Examples I, II and III of the '505 patent.

Example 14 of Depui '771 shows an omeprazole formulation identical in respect to the core material to those of Examples 2, 3, and substantially similar to that of Example 4, of the '505 patent. In the latter example, sodium lauryl sulphate has been replaced by a different but also well known surfactant, Pluronic F 68. In Example 14, the core material is further coated with a film coating polymer (hydroxypropylcellulose) used in a ratio of 8% whereas in Examples 2, 3 and 4 ('505 patent), the film forming coating polymer (HPMC or polyvinylpyrrolidone) is used in a 4 or 6% ratio.

Finally, in all the above cases, pellets with a separating layer are further coated with an enteric polymer used in an 8-10% ratio.

Again, the method to prepare omeprazole formulations of Example 14 Depui '771 and of Examples 2, 3 and 4 of the '505 patent is the same.

The formulations of Comparative Examples I, II and II are identical or substantially similar to those of Examples 2, 3 or 4 ('505 patent) <u>but lack the separating layer</u>.

Table 5 (column 14, lines 18 to 41) of the '505 patent lists various parameters such as acid resistance and storage stability of the Examples 2 to 8 preparations <u>(formulations with separating layer)</u> and of the Comparative Example I-V <u>(formulations without separating layer)</u>. This comparison shows stability problems or

unacceptable low resistance to dissolution in acid media of the formulations lacking the separating layer, whereas the preparations with a separating layer have good gastric juice resistance and stability (see column 14, lines 64-68 and column 15 lines 1 to 31 of the '505 patent).

All example pellets of Depui have a separating layer. Some of Depui's examples are identical or substantially similar to the preparations of the '505 patent. The '505 patent contains a side by side comparison of preparations with and without a separating layer and shows that those without a separating layer have problems. The Depui patent fails to inform as how to avoid the stability and acid resistance problems of the formulations lacking separating layers and therefore, one of skill in the art would not be encouraged, or expect from Depui in view of the '505 patent to prepare a stable formulation without a separating layer.

Therefore, the stability difference in the Depui formulation where the drug dosage form is prepared with and without a separating layer has already been established by the '505 patent which is of record

During the June 10, 2003 telephone interview, Applicants' undersigned counsel discussed using the above comparison to show that the disclosure of the Depui was insufficient and that one of ordinary skill in the art could not, based on the Depui reference, achieve a stable product. It is submitted that the above showing is sufficient. See *In re Fouche*, 169 U.S.P.Q. 429, 433 (CCPA 1971).

The above comparisons were again discussed with the Examiner during the November 6, 2003 telephone interview. The Examiner inquired why the now claimed dosage form does not degrade as does Comparative Example III of the Lovgren Patent ("the '505 patent"). She also stated that she did not see a difference between the dosage form described in the Lovgren '505 patent or the Depui reference, and the now claimed invention.

The now claimed dosage form without a separation layer between the active containing layer and the enteric coating is stable because the active layer is homogeneous and substantially non-porous. See pending claims 1, 34 and 36. This feature has been disclosed in the originally filed specification. Page 2, lines 12-19 of specification reads as follows:

Numerous techniques recently have been developed for preparing systems of release in the form of microgranules wherein the mixture of active ingredient and excipients is submitted to a process of kneading, extrusion, spheronization, coating, etc. Each of these pelletization techniques calls for a different technology, so that there are many types of pelletization equipment, coating pans or drums, fluid-bed equipment, extruders-spheronizers and centrifuging equipment, among others. The final result would appear to be the same, although there are in fact considerable differences between the pellets made using each technique. (underlining added)

Page 7, lines 1-5, of the original specification states:

In the present invention a formulation and a working methodology in a fluid bed of the "Wurster" type or the like have been developed. In it, the negative factors which affected the methods described to date are eliminated and substantial changes introduced with respect to the methods of previous patents for pellets containing benzimidazoles.

Page 8, lines 15-17, points out that:

The new galenical formulations object of the present invention are characterized in that they are spherical granules with a homogeneous active charge layer and a very unporous surface, formed by coating of an inert nucleus by spraying a single aqueous or hydroalcoholic mixture containing the active ingredient (anti-ulcer compound) together with the other excipients.

Page 9, lines 19 to 21, reads as follows:

When a single suspension-solution is projected onto the inert nucleus, a less porous and more homogeneous product is obtained than in the procedures known to date, and all the subsequent operations are simplified considerably. (Underlining added)

Also, on page 22 lines 1-2 and page 25, lines 13-14, it is disclosed that Photographs 4 and 8 show the low porosity and homogeneity of the coatings and the law of porosity accounts for the enhanced physical stability of the pellet.

Since the process is conducted in a single "Wurster" type fluidized bed coater, the claimed process need not use other pieces of equipment different from fluidized bed coaters of the Wurster-type or the like.

Neither Lovgren or either of the Depui references teaches the substantially spherical, stable oral formulation claimed of the present invention having a substantially non-porous, homogeneous, active layer, or how to produce them, or a process whereby such a product is obtained.

Neither Lovgren or either of the Depui references teaches that the substantially homogeneous, nonporous characteristics and substantially spherical shape of the granules comprising an inert core and active coating layer are result effective parameters which influence the stability of benzimidazole containing pellets or formulations.

Lovgren and Depui disclose preparation of pellets wherein the benzimidazole core material is made by extrusion/spheronization (see Examples 2 to 8 and Comparative Examples I to V of Lovgren and Examples 9 and 14 of Depui). Extrusion spheronization is a multi-step compaction process comprising dry mixing of the ingredients with excipients, wet granulation of the mass, extrusion of the wetted mass, charging the extrudates into the spheronizer to produce a spherical shape, drying the wet pellets in a dryer and, finally, screening to achieve the required size distribution.

Lovgren teaches that these extrusion/spheronization benzimidazole containing cores having a separating layer beneath the enteric coating, have good resistance to gastric juice as well as good stability whereas the same formulation lacking a separating layer (those of Comparative Examples I to V) experience at least one of stability problems or poor resistance to dissolution in acid media.

Depui also discloses the preparation of pellets by the powder-layering technique using a centrifugal fluidized coating granulator. See Depui Example 10. These pellets have a separating layer between the core material and the enteric coating.

An example of benzimidazole containing core prepared by powder-layering technique using a centrifugal fluidized coating granulator with enteric coating layer but lacking the separating layer is disclosed in Example 6 of Takeda's EP 642797 ("Takeda '797"):

Example 6

Production of a formulation comprising lansoprazole and a gastrointestinal mucosa-adherent solid preparation containing AMOX

1) Granules containing lansoprazole was prepared as follows.

Ingredients	mg
Lansoprazole	30
Magnesium Carbonate USP	22.4
Sugar Spheres NF	110.0
Sucrose NF	59.8
Starch NF	36.4
Low-Substituted Hydroxypropyl Cellulose NF (L-HPC-31)	40.0
Hydroxypropyl Cellulose NF (HPC-L)	1.4
Methacrylic Acid Copolymer LD (Eudragit L30D-55) (Röhm Pharma Co.)	44.6
Polyethylene Glycol NF (PEG-6000)	4.4
Titanium Dioxide USP	4.4
Polysorbate 80 NF (Rheodol TW-0120)	2.0
Talc USP	14.0
Colloidal Silicon Dioxide NF (Aerosil)	0.6
Purified water * USP	q.s.
Total	370.0

*: Removed during the manufacturing process
USP: The United States Pharmacopeia
NF: The National Formulary

Sugar spheres was coated with a mixture of lansoprazole, magnesium carbonate, sucrose, starch and L-HPC-31 by means of spraying aqueous HPC-L solution in a centrifugal fluid-bed granulator (CF-1000S, Freund Co.), and the resultant wet granules were dried in a vacuum oven at about 40°C for about 18 hours, and then sieved. The obtained granules were coated with aqueous enteric Eudragit suspension containing PEG-6000, talc, titanium dioxide and Rheodol TW-0120 in a fluid-bed coater (F10-Coater FLO-60, Freund Co.), and sieved, and then dried in a vacuum oven at about 42°C for about 18 hours. The obtained granules were mixed with talc and Aerosil.

2) 370 mg of granules containing lansoprazole as obtained in 1) above and 100 mg of gastrointestinal mucosa-adherent solid preparation containing AMOX as obtained in Reference Example 3 were packed in No.0 capsules to yield a capsule preparation.

The previously submitted Molina Declaration sets forth the attempts to reproduce Example 6 of Takeda '797. This experimental work led to the following conclusion:

"Therefore, even after correcting the defect of the procedure described in section 1) of example 6 of European Patent Application EP 0 642 797 in relation to the quantity of binder material, this procedure does not yield enteric-coated gastroresistant granules of lansoprazole that are appropriate and acceptable from the pharmaceutical standpoint. Consequently, the use of the above procedure does not yield granules equal or similar to those obtained with the procedure contemplated in Patent Application PCT WO 99/06032, particularly as described in example 1 therein."

Therefore, when enteric-coated gastroresistant benzimidazole granules are made by powder-layering technique using a centrifugal fluidized coating granulator without a separating layer between the active layer and the enteric coating, it results in granules having stability problems and unacceptable low resistance to gastric fluid. See Paragraph No. 5 of the Molina Declaration.

This kind of powder-layering process is carried out in a centrifugal bead granulator, shown below schematically:

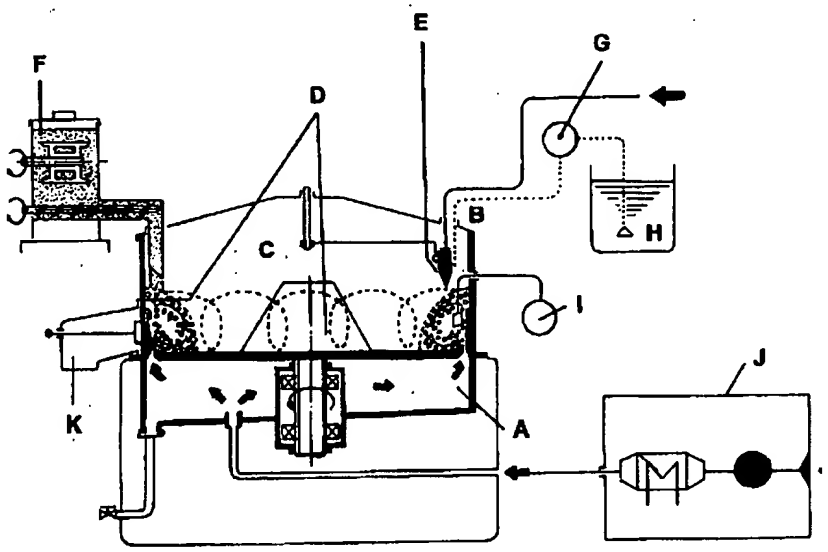


Figure 2. Schematic diagram of the centrifugal granulator. Key: Inlet air (A), Outlet air (B), Granulation chamber (C), Rotor (D), Solution spray system (E), Powder feeder (F), Liquid pump (G), Liquid vessel on a balance (H), Moisture sensor (I), Blow air generator system (J) and Product outlet (K) (modified from Goodhart 1989).

See the previously submitted selected pages of an academic dissertation on "Centrifugal granulation process for preparing drug-layered pellets based on microcrystalline cellulose beads", held at the University of Helsinki on April 2001. As previously advised, the complete text of the dissertation can be downloaded from:

http://ethesis.helsinki.fi/julkaisut/mat/farma/vk/rashid/centrifu.pdf

The schematic depicts a laboratory scale centrifugal fluid-bed granulator Freund CF-360EX, Freund Industrial Co., similar to the centrifugal fluid-bed granulator CF-1000S Freund Co. used in the Example 6 of Takeda '797.

As can be observed in the schematic, the beads are placed in a granulation chamber provided with a rotating plate at the bottom. The rotating plate centrifugally displaces the granules towards the chamber-wall, while the air flows by the plate edge. Simultaneously, the powder mixture is dosed from a powder feeder and the binding solution from a liquid vessel, producing a granulation process.

According to Takeda '797 Example 6, the granules after drying in an oven, are provided with an enteric coating by a subsequent coating process carried out in a fluidized-bed coater.

Applicant has already submitted technical trials which prove that by using the above process it is not possible to obtain pharmaceutically acceptable two-layered pellets , and this may very well be due to the structure of the resulting active coated pellets having a "raspberry" type structure, that is a porous, non-compact, non-homogeneous, open surface. Applicants have included a discussion of the effect of the coating procedures in prior Amendments and that discussion is incorporated by reference. Se for instance the Response Under Rule 111 of December 1, 2004 at page 15 to page 16, last line.

Depui Examples 1, 3, 4, 5 and 11, refer to the formation of pellets by suspension layering in a fluid bed apparatus but it is clear from the specification (col. 9, ll. 57 *et. seq.*) that Depui sees no relationship between any particular layering technique or conditions and the stability or gastric resistance of the resulting product.

An objective achieved by the present invention is a more simple and efficient process to obtain two-layered benzimidazole anti-ulcer pellets in form of substantially spherical granules provided with a substantially homogeneous non-porous active charge layer and an outer enteric layer, which are uniform and well shaped, having good friability and which are stable for an acceptable time period. See the present specification at pages 20, 24 and 25.

The solution proposed consists of coating the inert nuclei with a single solution-suspension containing the active ingredient, the binder and the other excipients of the first layer and, after drying, providing the obtained pellets with a second enteric layer, the coating operations being performed in a single Wurster-type or similar fluidized-bed coater.

Since none of the cited art (Lovgren nor Depui) teaches or suggests any relationship between the stability of pellets containing benzimidazoles and the characteristics of the active containing layer or spherical shape of the granules comprising benzimidazole or the coating technique one of ordinary skill in the art would not be motivated to prepare stable two-layered benzimidazole anti-ulcer pellets.

Without an inventive effort the skilled person would not be motivated to use the claimed process or have any reasonable expectation of success.

As indicated on page 1 of Attachment 2 to the December 12, 2003 Amendment After Final Rejection, significant amounts of solid material are processed using fluid-bed technology and one primary factor influencing a fluidized-bed process is airflow. Figure 1 of Attachment 2 shows the typical components of a fluid-bed processing unit. A fluid bed is a bed of solid particles with a stream of air or gas passing upwards through the particles at a rate great enough to set them in motion. Different types of bed are formed depending upon the movement of bubbles through the bed. See for instance, Example 3 of Attachment 2.

There are many kinds of fluidized bed apparatus. On page 4 of Attachment 3 (document downloaded from http://www.glatt-weimar.de/download/konti_ws_en.pdf) (December 12, 2003), there is an

example of a fluid bed useful for building up particles from powder-agglomeration or for liquid-granulation and to coat particles. All these processes can be accomplished by selecting air with different velocities in different chambers, selecting air temperatures and by the correct placement of the nozzles in the fluid bed.

None of the examples of Depui disclose the use of a Wurster-type or the like fluidized bed coater to form a substantially homogeneous non-porous active containing layer. The selection of this type of fluid bed equipment allows strict and automated control of the spraying and drying conditions necessary to apply the two layers to the inert core.

Further, as shown by the Johansson Declaration, following Depui's Example 5, but omitting applying the separating layer, resulted in pellets which showed rapid (within 1 hour) degradation of the active ingredient. As set forth in the Johansson Declaration, this rapid degradation was not unexpected based on the prior art. In contrast, the present specification shows that the now claimed products produced by the now claimed process have stability over extended periods. See the examples of the invention in the originally filed specification.

It is further submitted that the Johansson Declaration establishes that the presently claimed composition and process for making the same are unobvious in view of the prior art.

Claim 35 has been rejected under 35 U.S.C. 103(a) as unpatentable over Depui '771 in view U.S. Patent No. 4,853,230 to Lovgren et al. ("Lovgren '230"). It is submitted this rejection is also improper and should be withdrawn.

Lovgren '230 contains claims which are obvious in view of the claims of Lovgren '505. The disclosures of the '505 and '230 patents are substantially similar. Lovgren '505 is specific to omeprazole as the active ingredient while Lovgren '230 applies to substituted benzimidazoles as the active ingredient. Applicants' above discussion of Lovgren '505 is equally applicable to Lovgren '230.

Both Lovgren '505 and '230 teach the necessity of and claim a separating layer between the active containing core and the enteric coating. Therefore, to combine either of the Lovgren references with either of

the Depui references is improper since a vital and important part of the Lovgren references would have to be disregarded. By ignoring the necessary feature of the Lovgren references, the Examiner clearly is engaging in a pick and choose technique to formulate an obviousness rejection based on hindsight reconstruction. This is improper under 35 U.S.C. §103. Also see *In re Ratti*, 123 U.S.P.Q. 349 (CCPA, 1959). That Lovgren may suggest a single active ingredient does not remedy the deficiencies of Depui or provide motivation for the combination.

Claims 15 to 25, 31 to 34, 36, 39 and 40 have been rejected under 35 U.S.C. 103(a) as unpatentable over Depui '771 in view of U.S. Patent No. 4,017,647 to Ohno et al. ("Ohno") or U.S. Patent No. 2,799,241 to Wurster. It is submitted these rejections are improper and should be withdrawn.

Depui '771 has been discussed above. Apparently, the Examiner cites Ohno for providing an enteric coating on a solid dosage form. The rejection seizes on a phrase from column 3, lines 24-40 taken out of context from the Ohno reference.

The objective of the Ohno disclosure is to enteric coat a dosage form with an aqueous solution of a polymeric substance having carboxyl groups as a water soluble salt and contacting the coated dosage form with an inorganic acid to covert the polymer substance into the water insoluble acid form. The reference not teach or suggest that the results obtained by all coating apparatus are equivalent. Ohno does not provide a broad teaching of equivalency. The Examiner is not free to modify the disclosure so as to suggest that which the actual text does not. The citation of Ohno highlights that the prior art did not appreciate the significance of the procedure by which the active layer is applied.

The Office Action asserts that Wurster teaches that a Wurster-type fluidized apparatus provides a uniform coating preventing a coating material from sticking to the inner surface of the chamber.

Applicants do not deny that a Wurster-type fluidized apparatus was known. However, what is not disclosed or suggested in any of the references is that by utilizing this type of apparatus, one can obtain a substantially non-porous homogeneous soluble active layer which can eliminate the need for a separating layer

in those types of formulations where the prior art required the presence of the separating layer to protect the active ingredient from the deleterious affects of enteric coatings. None of the cited art provides a disclosure or suggestion of such a feature or how to obtain it.

Claims 1 to 13, 26 to 29, 37 and 38 have been rejected under 35 U.S.C. 103(a) as unpatentable over Depui '184. It is submitted this rejection is also improper and should be withdrawn.

The obviousness rejection based on Depui '184 is largely a repeat of the prior rejections based on the Depui '771 reference. Accordingly, Applicants refer to the prior comments regarding the '771 reference. Also Applicants' Remarks regarding the other obviousness rejection(s) based on Depui '771 alone or in combination should be considered to be set forth in traversal of this rejection.

Reply to Examiner's Response to Previously Submitted Arguments

The Examiner's response to the previously submitted arguments gives the impression that she may have misconstrued or misunderstood Applicants' argument. Applicants do not contest that Depui discloses the need for an enteric coating. It is obvious that Depui has an enteric coating layer. Applicants' position is that although Depui refers to a separating layer (that layer between the active ingredient and the enteric coatings) as "optional", there is no description of such an embodiment and no disclosure as to how to obtain a stable benzimidazole formulation without the use of the separating layer. See discussion *supra* regarding lack of identity and enablement.

Applicants will address the Examiner's response to the previously submitted arguments using the numbering of the Examiner.

1. The Examiner suggests that because the components that constitute the active layer are nonporous that she is free to rely on inherency.

First, nothing of record establishes that the components are "non-porous". Further, the claim limitation does not state that the materials from which the active layer is made are nonporous. Rather, the layer that

contains the active ingredient is substantially homogeneous and nonporous. Thus, the Examiner has no basis to rely on inherency. Inherency is only proper when a feature or condition must result not when it is merely a possibility.

2. Again, the Examiner's comments fail to address the issue. The issue is not whether any of the substances are or are not alkaline. The issue relates to the failure of the reference to show or enable a stable dosage form without a separating layer. Further, the owner of the '505 patent which is also the owner of the Depui patents, has asserted that even impurities in a substance can constitute an alkaline material. Whether the listed ingredients in Example 5 themselves are alkaline or contain residual alkaline impurities does not alter the fact that the reference does not disclose or enable a stable dosage form of the benzimidazole compounds without a separating layer.

The Examiner has previously quoted from the Webster dictionary as to the meaning of "optional". None remedy Depui's deficiencies. It is improper to attempt to supplement a disclosure by referring to dictionary definitions. In any event, the mere use of "optimal" does not in and of itself mean that an otherwise undescribed embodiment is identified or enabled. If that were the case, a patentee could use many words in a specification or repeatedly use "optional" without enabling those embodiments and thus preclude subsequent applicants from obtaining patent protection on improvements which were never enabled by the patentee's disclosure. Depui does not disclose how to obtain a stable formulation without a separating layer.

The Examiner's citation to *In re Petering* is not relevant to the issue here. That one can "envision an embodiment" does not does mean that that embodiment is enabled. The issue *In re Petering* was whether a reference, by a generic disclosure which embraced literally tens of thousands of compounds, actually anticipated certain specific compounds within the scope of the genus based on that reference disclosure. That is not the issue here.

The Examiner argues that a patent disclosure is not limited to an example or to a preferred embodiment. While that may be true, that does not permit a patentee to broadly refer to a possible

embodiment but fail to contain disclosure commensurate in scope sufficient to enable that embodiment. This is especially true where, in prior art owned by the same assignee, the necessity for a separating layer has been shown. See Applicants' above discussion of the Lovgren '505 and '230 patents. An invitation to experiment does not amount to anticipation.

3. The Examiner states that she is unclear as to why the applicants refer to Lovgren's disclosure when addressing arguments based solely on Depui stating that Depui does not incorporate Lovgren's disclosure by reference. As discussed above, Depui does refer to the Lovgren patent. Further Lovgren provides evidence which contradicts the Examiner's position or places in perspective Depui's lack of invention of an optional feature. The Examiner has not yet considered this evidence. This is error, *See In re Piasecki and Myers*, 223 USPQ 785, 788 (Fed. Cir. 1984):

> When prime facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over..

Further, Lovgren '505 is part of the relevant prior art and thus should be considered not only as evidence because of the tests reported in Lovgren but also as part of the prior art since the art must be considered "as a whole" under 35 U.S.C. §103.

Applicants cannot follow the reasoning of Examiner's position that because she believes Example 5 of the Depui does not include an alkaline material in the core that the Example 5 of Depui enables an embodiment without a separating layer. It is crystal clear from Example 5 that a separating layer is utilized in Depui's '771 in column 17 at about line 63. The Examiner is not free to rewrite the examples of a reference.

The Examiner appears to be of the opinion that because she has cited a reference for only one specific purpose that that is the only purpose or basis for which that reference can be considered. This is in direct violation of 35 U.S.C. 103 that requires the art be considered as a whole. Applicants have set forth in significant detail the teachings of the Lovgren reference. For instance, as indicated above, Example 1 of the Lovgren '505 patent contains a comparative showing which illustrates that those formulations without a

separating layer do not have sufficient stability with respect to the proton pump inhibitors such as benzimidazole. This prior art information is of record in this case and must be fully considered whether the Examiner has relied on that part of the Lovgren '505 reference or not. See, *In re Piasecki, supra.*

The question here is not whether the secondary reference should be removed. The issue, which the Examiner has never addressed throughout this prosecution, is that Lovgren '505 teaches the necessity of a separating layer. The language of Depui which merely refers to the separating layer as "optional" but which fails to disclose an embodiment where no separating layer is present, is undermined by the teachings of the prior art. Thus, Lovgren whether combined with Depui for purposes of the '103 rejection or, whether submitted by Applicants to establish the lack of enablement by Depui, is a reference of record and must be considered.

The Examiner's comments with respect to the Lovgren formulation are not understood. If the Examiner is indicating that the 103 rejection based on Depui does not permit Applicants to rely on Lovgren to show that the art teaches away from the now claimed invention, this is a direct violation of 35 U.S.C. 103 that the art be considered as a whole. If the Examiner is referring to the rejection based on Depui under 35 U.S.C. 102, Lovgren is submitted to show that the Depui references lack enablement.

4. The Examiner states that the Wurster-type fluidize bed limitations are only recited in the process claims not the product claims and she therefore concludes that the argument is moot. However, the Examiner has rejected the process claims on the same art, applied in the same manner, as applied to the product claims. Further, the Examiner is impermissibly reading disclosure into the Depui reference, disclosure which is not there and which the Examiner should not be attempting to rely on. The Examiner is thus rewriting the specification of the reference. That is impermissible.

5. The Examiner indicates the question of stability is one of degree. While in a broad sense such a statement may be true, the point here is that to obtain a pharmaceutical dosage form, one must meet certain stability requirements. Claims 38 to 40 recite that the dosage form is stable. Further, the specification contains sufficient information to show the minimum stability requirements. The Examiner states that such features

(minimum stability requirements) are not recited in the claim. However, such features need not be recited in a claim. See, *Preemption Devices, Inc. v. Minnesota Mining and Manufacturing Company*, 221 U.S.P.Q. 841, 844 (Fed. Cir., 1989).

6. The phrase "consisting essentially of" is interpreted in light of the specification. It is clear, that in the present invention, and from the claim language, that the phrase "consisting essentially of" cannot be interpreted to permit an applied separating layer. Under the Examiner's reasoning, use of phrases such as "consisting essentially of" would render the cited limitations meaningless because each positive limitation would have to be accompanied by a comprehensive list of exclusions from that limitation. Such is not the way a claim is interpreted and is obviously impractical on its face.

Starting on page 16 of the March 4, 2005 Office Action, the Examiner responds to arguments based on the Section 103 rejection based on Depui in view of Lovgren. It is submitted that Applicants' above comments have addressed the Examiner's response to the argument previously submitted with respect to that combination of references.

On page 17, the Examiner provides a response to the arguments based on the Section 103 rejection based on Depui in view of Ohno. It is believed that Applicants have addressed the Examiner's response in the above comments.

The Examiner's conclusion that it is obvious for one of ordinary skill in the art to manipulate conditions to obtain the best possible results is not understood. The Examiner fails to identify which parameters she is referring to or where the prior art teaches that such undefined parameters could be manipulated or what would be expected. If the prior art does not predict or identify parameters as result effective, there is no motivation to manipulate those parameters. See, *In re Sebek*, 175 U.S.P.Q. 93 (CCPA, 1972).

The Examiner has failed to establish anticipation, obviousness or motivation to combine the references. Further, the Examiner has not considered previously submitted proofs. Thus, the issuance of a

Final Rejection is improper. In addition, the Examiner has not complied with Applicants' repeated requests for compliance with 37 CFR § 1.104(d)(2).

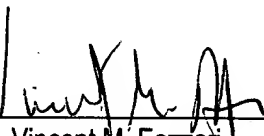
In view of the foregoing, withdrawal of the Final Rejection, reconsideration and allowance of the application with claims 1 to 13 and 15 to 40 are earnestly solicited.

The Examiner is invited to phone Applicants' undersigned attorney after receiving the foregoing to resolve any remaining issues.

If there are any additional fees or charges are required at this time in connection with the present application; the same they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,

COHEN, PONTANI, LIEBERMAN & PAVANE

By 

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